CCR5 in 'stopgap' antiviral measure

After secondary respiratory virus infection, but before the generation of secondary memory CD8$^+$ T cells, protective primary memory CD8$^+$ T cells infiltrate mouse airways. In *Immunity*, Woodland and colleagues designate CCR5 as the chemokine receptor responsible for this transient protection. Two days after secondary virus infection, the number of primary memory CD8$^+$ T cells and the concentration of CXCR3 and CCR5 chemokines increase in the airways. However, although abundant on the surface of primary memory CD8$^+$ T cells, CXCR3 is dispensable for their airway recruitment after virus challenge. Presumably as a result of inflammatory cytokine production, CCR5 expression increases transiently on primary memory CD8$^+$ T cells in secondary lymphoid organs of virus-challenged mice, and it is required for their trafficking to the airways. CCR5-deficient mice showed higher viral titers immediately after secondary virus infection. Unknown is whether CCR5 influences CD8$^+$ T cell responses during other airway inflammatory disorders. ***CB***
***Immunity* 29, 101–113 (2008)**

Tat on the brain

The brain microvasculature differs from other vascular beds in the presence of 'tight' junctions that restrict permeability. Yet HIV can readily breach the 'blood-brain barrier' by disrupting these tight junctions. In the *Journal of Neuroscience*, Zhong *et al.* show that purified HIV-1 Tat protein induces cytoskeletal changes in cultured human brain microvascular endothelial cells by stimulating rapid caveolin-1 activation and signaling via Ras to downstream mediators. Tat exposure leads to downregulation of the transmembrane protein occludin and accessory proteins, zonula occludens ZO-1 and ZO-2, which are necessary for maintaining tight junctions. Inhibition of Ras signaling or knockdown of caveolin-1 abolish the Tat sensitivity. These data suggest circulating Tat can alter brain microvascular permeability, easing the barrier posed against HIV-1 and inflammatory cell passage into the brain. *LAD*
J. Neurosci. **28**, 7788–7796 (2008)

Gatekeepers

Vascular endothelial-cadherin (VE-cad) transmembrane molecules contribute to barrier function at endothelial cell junctions. VE-cad surface expression is regulated by intracellular p120-catenin, but whether this interaction also influences leukocyte transmigration is not clear. In *Blood*, Alcaide *et al.* show that overexpression of p120-catenin inhibits leukocyte transmigration by preventing VE-cad displacement from the junctions, thereby preventing gaps through which leukocytes can migrate. Tyrosine phosphorylation of VE-cad, which occurs upon ICAM-1 engagement, is inversely correlated with p120-catenin abundance. Overexpression of p120-catenin blocks VE-cad phosphorylation and leukocyte transmigration, as does expression of a nonphosphorylatable VE-cad mutant. Contrary to previous hypotheses, VE-cad is not internalized at the gaps formed during transmigration, but rather lateral displacement seems to occur. These data suggest endothelial junctions are regulated by competition between p120-catenin and tyrosine kinases for interaction with VE-cad. ***LAD***
***Blood* (18 July 2008) doi:10.1182/blood-2008-03-147181**

Written by Christine Borowski, Douglas C. Braaten & Laurie A. Dempsey

Fractalkine-induced transmigration

Human endothelial cells can present antigen directly to CD4$^+$ effector memory (EM) T cells to trigger proliferation and cytokine production *in vitro* as well as graft rejection in transplant settings. In the *Journal of Immunology*, Manes and Pober reveal differences between activated dermal microvascular and large vein endothelial cells in their ability to trigger transmigration of antigen-specific EM cells. TCR engagement under shear stress, mimicking blood flow, triggers formation of a 'finger-like' transendothelial protrusion before actual transmigration through the endothelial layer. Neither naive nor central memory CD4$^+$ T cells form such protrusions, and they do not transmigrate under similar conditions. This process requires expression of ICAM-1 and the transmembrane chemokine CX3CL1, also known as fractalkine, which is recognized by CX_3CR1, expressed only by the EM subset of CD4$^+$ T cells. Further work is required to explore this diapedesis pathway. *LAD*
J. Immunol. **180**, 8386–8392 (2008)

Sialylation in leukocyte arrest

Although post-translational glycosylation is required for selectin ligand and chemokine receptor function during leukocyte recruitment, specific glycosyltransferases required for leukocyte arrest are not well known. In *Journal of Experimental Medicine*, Sperandio and colleagues demonstrate that sialylation of the chemokine receptor CXCR2 by the glycosyltransferase ST3Gal-IV is essential for chemokine-triggered neutrophil arrest *in vivo*. Upon tumor necrosis factor stimulation, exteriorized cremaster muscle venules from ST3Gal-IV–deficient mice demonstrate defective L- and E-selectin–dependent leukocyte rolling, adhesion and extravasation after injection of the CXCR2 ligands CXCL1 or CXCL8. Carboxyfluorescein-labeled CXCR2 ligands bind much less to neutrophils from ST3Gal-IV–deficient mice or to wild-type mouse and human neutrophils treated with neuraminidase, which removes surface sialic acid. Microflow chamber assays show that ST3Gal-IV contributes to arrest of leukocytes in response to CXCL1. These data demonstrate the importance of ST3Gal-IV–dependent sialylation of CXCR2 in mediating leukocyte arrest during inflammation. ***DCB***
***J. Exp. Med.* 205, 1435–1446 (2008)**

gp130 cytokine tag team

Interleukin 6 (IL-6) suppresses neutrophil infiltration into acute inflammatory sites, thereby paving the way for a subsequent influx of mononuclear leukocytes. In the *Journal of Immunology*, Jones and coworkers show that the cytokine oncostatin M (OSM), although similar to IL-6 in its dependency on the gp130 signal transducer, suppresses mononuclear leukocyte infiltration. After intraperitoneal injection of *Staphylococcus epidermidis* supernatant, mice lacking OSMRβ—which forms a heterodimer with gp130 to transduce OSM signals—show increased numbers of infiltrating monocytes, but similar numbers of neutrophils, in the peritoneum. Compared to wild-type counterparts, *S. epidermidis*–challenged OSMRβ-deficient mice contain higher peritoneal concentrations of the chemokine CCL5—a factor established as capable of promoting monocyte recruitment—and show stronger peritoneal activation of NF-κB. Further work is needed to understand how IL-6 and OSM work cooperatively and/or antagonistically in situations of health and disease. *CB*
J. Immunol. **181**, 2174–2180 (2008)